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Pre-diagnostic and post-diagnostic psychopharmacological treatment of 16 288 patients with bipolar disorder

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Abstract

Objectives: The aim was to describe the pre-diagnostic and post-diagnostic psychopharmacological treatment of bipolar disorder over the past two decades.

Methods: We identified all 16 288 individuals aged ≥ 18 years, who received their first diagnosis of bipolar disorder at a psychiatric hospital in Denmark between 1997 and 2014. For each calendar year, we calculated the proportion of patients (with index date in the respective calendar years) who were prescribed psychopharmacological treatment in the 2 years preceding and the 2 years following the date of the first diagnosis of bipolar disorder. For patients diagnosed with bipolar disorder from 2007 to 2010 (n = 3949), we described the psychopharmacological treatment from 1995 to 2016, that is, from up to 16 years prior to and up to 10 years after the diagnosis.

Results: Concomitant use of ≥ 2 antidepressants in the 2 years preceding the bipolar disorder diagnosis increased over the study period. In the 2 years following the diagnosis, the use of lithium decreased, while use of atypical antipsychotics (particularly quetiapine), valproate, and lamotrigine increased over the study period. During the 10 years following the diagnosis, 53%-90% of the patients received any psychotropic drug while 12%-26% received treatment with an antidepressant without overlapping treatment with a mood-stabilizing drug.

Conclusion: The increased use of two or more antidepressants suggests more focus on bipolar disorder as a differential diagnosis to treatment-resistant unipolar depression. The decreased use of lithium (consistent with international trends) and the prevalent use of antidepressants without overlapping treatment with a drug with mood-stabilizing properties are concerning.

KEYWORDS

antidepressive agents, antipsychotic agents, bipolar disorder, drug utilization, lithium, mood stabilizer, pharmacoepidemiology, psychopharmacology

1 | INTRODUCTION

Bipolar disorder is a severe mental disorder characterized by recurrent episodes of depressive, hypomanic, manic, and mixed episodes. The first-line pharmacological treatment for bipolar disorder is a mood-stabilizing drug.[1-3] Lithium was the first drug with established mood-stabilizing properties and has been a cornerstone in the treatment of bipolar disorder since the 1960s.[4] However, lithium has a relatively narrow therapeutic window, requires regular blood testing, and long-term use (with high doses) is associated with potentially severe side effects.[5,6] Therefore, mood-stabilizing antipsychotic and antiepileptic drugs with different side effect profiles that do generally not require regular blood testing have become increasingly popular alternatives to lithium over the past decades.[3,7,8] Maintenance treatment of bipolar disorder using either lithium or a mood-stabilizing antipsychotic or antiepileptic drug is in line with current international treatment guidelines.[1-3]

It is widely known that drug-prescribing practices do not always match the advice provided by clinical guidelines based on the best available evidence.[9,10] Therefore, a number of studies of the "real-world" treatment of bipolar disorder have been conducted.[7,8,11-19] However, none of these studies provide the full picture as they have either (i) focused exclusively on a subtype of patients with bipolar disorder,[8,16] (ii) covered few years of observation [7,12-14,17-19] (iii) focused only on specific drugs,[17,18] (iv) not reported data on potentially harmful polypharmacy [12,15,18,19] or the controversial practice of treating with an antidepressants without overlapping treatment with a drug with mood-stabilizing properties,[7,12,15,17,19] and (v) not investigated the psychopharmacological treatment in the period preceding the diagnosis of bipolar disorder, during which many patients are highly symptomatic.[11,20-22]

For these reasons, we conducted a comprehensive, longitudinal study of all patients diagnosed with bipolar disorder at psychiatric services in Denmark in the period from 1997 to 2014. Specifically, we had the following aims:

1. To characterize the changes in the psychopharmacological treatment of bipolar disorder over the past two decades.
2. To assess the psychopharmacological treatment in the 2 years prior to—and two years after the first diagnosis of bipolar disorder—with particular emphasis on polypharmacy and treatment with antidepressants.
3. To describe the psychopharmacological treatment up to 16 years prior to—and up to 10 years after the diagnosis of bipolar disorder—in the subset of patients diagnosed in the period from 2007 to 2010.

2 | METHODS

We performed a population-based cohort study based on data from the nationwide Danish registers. The linkage of data from the registers described below (at the level of the individual) is enabled by the unique personal registration number, which is assigned to all legal residents in Denmark and registered in the Danish Civil Registration System.[23] The use of these data has been approved by the Danish Data Protection Agency and Statistics Denmark. Approvals from ethical review boards are not required for register-based studies.

2.1 | Study population

The Danish Psychiatric Central Research Register [24] has registered all inpatient contacts to psychiatric hospitals since 1969 as well as all outpatient and emergency room contacts since 1995. All assigned diagnoses were coded in accordance with the International Classification of Diseases 8th edition (ICD-8) until December 31, 1993, and in accordance with the ICD-10 since then. For this study, we identified all adults (≥18 years) who were registered in the Danish Psychiatric Central Research Register with their first bipolar disorder diagnosis (ICD-10: F30-31) following inpatient or outpatient treatment in the period from January 1, 1997 to December 31, 2014. In order to obtain a population with incident, adult-onset bipolar disorder, we excluded individuals diagnosed with bipolar disorder (ICD-8:296.19, 296.39, 298.19/ICD-10: F30-31) prior to January 1, 1997 or before the age of 18, or a schizophrenia-spectrum disorder (ICD-8:295.X9, 296.89, 297.X9, 298.29-298.99, 299.04, 299,05, 299.09, 301.83/ICD-10: F20-F29) prior to the bipolar disorder diagnosis. Among the identified individuals with bipolar disorder, the date of first diagnosis (the index date) was either the date of initiation of an outpatient contact among patients diagnosed in outpatient settings or the date of discharge among patients diagnosed during an admission.

2.2 | Baseline characteristics of the sample

We extracted the following data at the index date: age, sex, educational level (primary school only or higher education),[25] inpatient or outpatient diagnosis, bipolar subtype (based on the ICD-10), calendar year of diagnosis, use of a cardiovascular drug in the year prior to the index date (Anatomical Therapeutic Chemical (ATC) codes: C01-C10),[26] any cardiovascular disease registered in the Danish National Patient Registry since 1977 (ICD-8:390-449, 450-458/ICD-10: I00-I99),[27] the presence of a chronic medical disease as defined by the Charlson Comorbidity Index,[28] and parental mental disorders registered since 1969 (not possible for the oldest age groups).[24]

2.3 | Assessment of psychopharmacological treatment prior to and after the diagnosis of bipolar disorder

For each individual, we extracted information on prescriptions redeemed in the 2 years prior to the index date of the diagnosis of bipolar disorder as well as the 2 years following it. These data were available from the Danish National Prescription Registry,[26]

which contain information on all prescriptions redeemed at Danish pharmacies since January 1, 1995 including the daily defined dose (DDD) and the ATC code. Data on the redeemed prescriptions from the following drug classes (ATC codes) were extracted: antidepressants (N06A), antipsychotics (N05A excluding N05AN01) divided into atypical and typical, lithium (N05AN01), mood-stabilizing anticonvulsants (carbamazepine [N03AF01], oxcarbazepine [N03AF02], valproate [N03AG01], lamotrigine [N03AX09], gabapentin [N03AX12]), benzodiazepines (N05BA, N03AE01), and hypnotics (N05C). We also identified redeemed prescriptions for the most frequently used drugs within these classes, for example, valproate or quetiapine. A detailed list of all ATC codes/drugs is provided in Table S1. The term "mood stabilizer" covers lithium and mood-stabilizing anticonvulsants (antipsychotic drugs were assessed separately).

Furthermore, we assessed whether drugs from different classes were used at the same time, that is, the prevalence of combination therapy (hypnotics were not included in the calculation of combination therapy). This was carried out by calculating the treatment length for each redeemed prescription via the following formula: DDD*1.15 + 7. The multiplication of 1.15 and the addition of 7 days allows for individual differences in doses and up- and down-titrating regimens, which is closer to real-world treatment dosages.[29] Combination therapy was defined as use of at least two drugs (different ATC codes) overlapping for more than 30 days. We also assessed specific classes of drugs that were used concomitantly, for example, a mood stabilizer with an antipsychotic or an antidepressant with an antipsychotic. Treatment with an antidepressant without overlapping treatment with a mood-stabilizing drug was defined as use of at least one antidepressant drug for more than 30 days without concomitant use of a drug with mood-stabilizing properties (ie, no concomitant use of lithium, antipsychotic drugs, or mood-stabilizing anticonvulsants in these 30 days).

For the subpopulation of individuals diagnosed with an index date for bipolar disorder in the period between 2007 and 2010, we extracted information on prescriptions redeemed in up to 16 years before—and up to 10 years after the index date.

For individuals registered with a diagnosis of a schizophrenia-spectrum disorder (ICD-10: F20-F29) after the index date, the follow-up in terms of pharmacological treatment was censored at the date of this diagnosis.

2.4 | Statistics

The annual incidence of bipolar disorder was calculated as the number of individuals with (incident) bipolar disorder divided by the number of Danish residents aged 18 years or above at the end of each calendar year. The characteristics of the population are shown via descriptive statistics, that is, proportions for categorical variables and medians (with interquartile ranges [IQR]) for continuous variables.

For each calendar year from 1997 to 2014, we calculated the proportion of individuals with bipolar disorder (with index date in the respective years), who had redeemed at least one prescription for the drugs of interest during the 2 years preceding as well as the 2 years following the index date. Since the treatment of bipolar disorder likely differs depending on age due to, for example, medical comorbidity, we included analyses that were stratified on the age of diagnosis categorized as follows: 18-29 years, 30-44 years, 45-59 years, and ≥ 60 years.

Within the subset of the cohort with a bipolar disorder index date in the period from January 1, 2007 to December 31, 2010, we calculated the proportion of patients that had redeemed at least one prescription per year for the above-mentioned psychotropic drugs in up to 16 years before their first-time diagnosis (ie, 1995 until 2010) and up to 10 years after their diagnosis (ie, from 2007 to 2016). In this assessment of drug use prior to the diagnosis of bipolar disorder, we only included individuals (and their redeemed prescriptions) if they were at least 10 years old in the year of interest.

Due to the very large sample size, we refrained from running statistical analyses on the trends in the proportion of patients using the various drugs over the study period, as even very subtle changes would turn out to be statistically significant.

STATA version 15 and R version 3.5.2 [30] were used for all analyses. Data are not available due to Danish data protection regulations.

2.5 | Sensitivity analyses

We repeated all analyses for medication use in the 2 years preceding and following the diagnosis of bipolar disorder for the following subgroups: females, males, individuals with a prior diagnosis (assigned at a psychiatric hospital) of mental disorder (ICD-8:290-315; ICD-10: F00-99), individuals without any prior diagnosis (assigned at a psychiatric hospital) of mental disorder, and those with a prior diagnosis (assigned at a psychiatric hospital) of unipolar depression (ICD-8:296.09, 296.29, 298.09, 300.49; ICD-10: F32-33).

3 | RESULTS

We identified 16 288 adults who were born before January 1, 1997 and received their first diagnosis of bipolar disorder after turning 18 years within the period from January 1, 1997 through December 31, 2014. The characteristics of the sample at the time of the diagnosis of bipolar disorder are shown in Table 1.

The incidence of diagnosed bipolar disorder increased from 1997 (1.2/10 000) to 2014 (2.9/10 000)—among both females (1.4/10 000 to 3.5/10 000) and males (0.9/10 000 to 2.4/10 000) (Figure 1). The mean age at the first diagnosis of bipolar disorder decreased from 54.5 years in 1997 to 40.8 in 2014.

A total of 9628 (59%) of the individuals with bipolar disorder had previously been diagnosed with a mental disorder at a psychiatric hospital (unipolar depression in 6346 [66%] of these cases). In the 2 years prior to the diagnosis of bipolar disorder, 3772 (23%) of the individuals had been admitted to a psychiatric hospital with a mean duration of admission(s) of 39 days (IQR = 4-51 days).

TABLE 1 Characteristics of 16 288 adults at the time of their first bipolar disorder diagnosis

	Age 18-29		Age 30-44		Age 45-59		Age ≥ 60	
Total, N (%)	3208	19.7	4931	30.3	4576	28.1	3573	21.9
Sex, N (%)								
Female	1998	62.3	2899	58.8	2387	52.2	2089	58.5
Male	1210	37.7	2032	41.2	2189	47.8	1484	41.5
Mean age ± SD	24.4	±3.3	37.5	±4.2	52.1	±4.2	71.4	±8.3
Episode at first diagnosis, N (%)								
Hypomania	103	3.2	163	3.3	158	3.5	149	4.2
Mania without psychotic features	106	3.3	171	3.5	218	4.8	237	6.6
Mania with psychotic features	169	5.3	227	4.6	213	4.7	183	5.1
Depression, mild to moderate	187	5.8	303	6.1	187	4.1	119	3.3
Depression, severe without psychotic features	55	1.7	89	1.8	95	2.1	53	1.5
Depression, severe with psychotic features	21	0.7	24	0.5	35	0.8	40	1.1
Mixed episode	104	3.2	147	3.0	130	2.8	54	1.5
Currently in remission	116	3.6	153	3.1	144	3.2	97	2.7
Other bipolar disorder	113	3.5	147	3.0	142	3.1	94	2.6
Unspecified bipolar disorder	2092	65.2	3391	68.8	3211	70.2	2488	69.6
Bipolar disorder II	248	7.7	290	5.9	190	4.2	147	4.1
Setting, N (%)								
Inpatient	1127	35.1	2329	47.2	2816	61.5	2534	70.9
Outpatient	2081	64.9	2602	52.8	1760	38.5	1039	29.1
Prior diagnosis of mental disorder, N (%)	1681	52.4	2892	58.7	2838	62.0	2217	62.1
1996-2000	110	42.2	308	54.4	477	60.8	505	62.4
2001-2005	209	45.9	517	55.2	674	60.6	564	59.9
2006-2009	396	56.7	719	60.7	642	62.5	505	62.9
2010-2014	966	53.9	1348	60.1	1045	63.3	643	63.0
Time since first psychiatric contact, Years ± SD	3.3	±4	6.4	±6.1	10.1	±9.7	15.1	±12.3
1996-2000	2.2	±2.3	5.9	±6.3	10.7	±9.2	13.3	±10.2
2001-2005	2.9	±2.9	5.8	±6	10.5	±9.7	14.2	±11.3
2006-2009	3.8	±3.7	6	±5.7	9.6	±10	15.8	±12.7
2010-2014	4.4	±4.4	6.9	±6.3	10	±9.8	16.7	±14.1
Calendar year of diagnosis, N (%)								
1996-2000	261	8.1	565	11.5	785	17.2	809	22.6
2001-2005	455	14.2	937	19.0	1112	24.3	941	26.3
2006-2009	699	21.8	1185	24.0	1027	22.4	803	22.5
2010-2014	1793	55.9	2244	45.5	1652	36.1	1020	28.6
Cardiovascular comorbidity, N (%)								
Cardiovascular drug use	161	5.0	639	13.0	1430	31.3	2132	59.7
Any cardiovascular disease	144	4.5	538	10.9	1044	22.8	1528	42.8
Charlson chronic somatic diseases, N (%)								
0	2912	90.8	4347	88.2	3559	77.8	2024	56.7
1+	296	9.2	584	11.8	1017	22.2	1549	43.3
Family history of mental disorders, N (%)								
Mother any mental disorder	626	19.5	900	18.3	618	13.5	70	2.0

(Continues)

TABLE 1 (Continued)

	Age 18-29		Age 30-44		Age 45-59		Age ≥ 60	
Mother bipolar disorder	151	4.7	130	2.6	99	2.2	7	0.2
Mother unipolar depression	294	9.2	408	8.3	316	6.9	33	0.9
Father any mental disorder	490	15.3	690	14.0	395	8.6	27	0.8
Father bipolar disorder	94	2.9	105	2.1	43	0.9	<5	n.a.
Father unipolar depression	173	5.4	245	5.0	163	3.6	6	0.2

Abbreviations: ICD-10, International Classification of Diseases, 10th edition; n.a., not applicable (According to Danish law, this number cannot be reported due to too few cases and the resulting risk of identification); SD, Standard deviation.

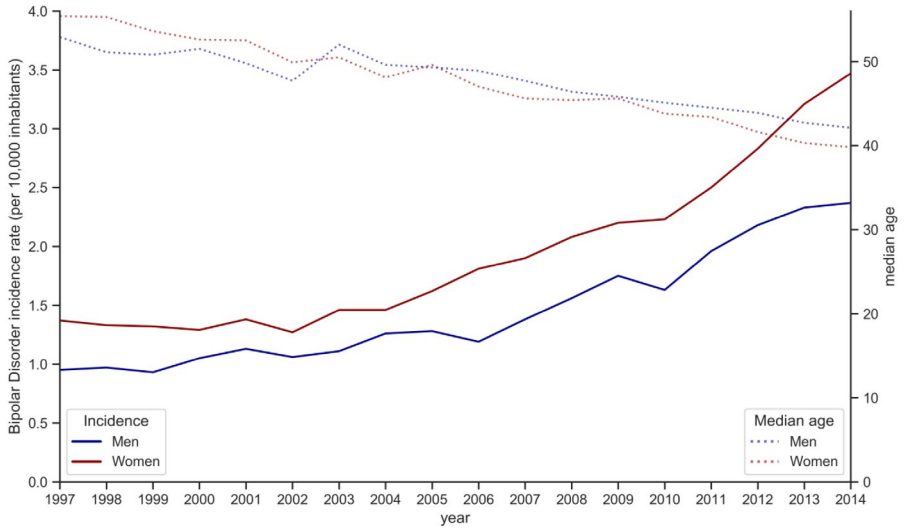


FIGURE 1 Yearly incidence rates of diagnosed bipolar disorder including the median age at diagnosis in the period from 1997 to 2014, shown separately for men and women

In the 2 years following the diagnosis of bipolar disorder, a total of 5776 (35%) of the individuals were admitted to a psychiatric hospital with a mean duration of admission(s) of 59 days (IQR = 12-74). Of those, 3865 (67%) were admitted due to bipolar disorder (ICD-10: F30-31) and 1069 (19%) due to substance use disorder (F10-19). A total of 800 (5%) were diagnosed with a schizophrenia-spectrum disorder in the 2 years following the bipolar disorder diagnosis (ICD-10: F20-29).

Figures 2 and 3 show the proportions of use of the respective psychotropic drugs for the index years of the diagnoses, meaning that people diagnosed for the first time in 1997 had the pattern of use shown for the year 1997 for the 2 years before (top panels) and the 2 years after (lower panels). The results from the sensitivity analyses (data for females, males, individuals with a prior diagnosis of mental disorder, individuals without any prior diagnosis of mental disorder, and those with a prior diagnosis of unipolar depression) are shown in Figures S1-S6.

3.1 | Psychopharmacological treatment prior to the diagnosis of bipolar disorder in 1997-2014

The proportion of individuals using any type of psychotropic drugs (red line in the top panel of Figure 2A) in the 2 years prior to being diagnosed with bipolar disorder remained rather stable in the period from 1997 to 2014 across all age groups. However, large changes were observed for the various classes of drugs and for individual drugs. The most prominent changes were that (i) the use of typical antipsychotics seemed to be replaced by use of atypical antipsychotics (Figure 2A)—especially quetiapine (Figure 3B); (ii) the use of benzodiazepines was reduced (Figure 2A); (iii) the use of serotonin-norepinephrine reuptake inhibitors (SNRIs) and noradrenergic and specific serotonergic antidepressants (NASSAs) increased while the use of tricyclic antidepressants (TCAs) was reduced (Figure 3C); and the concomitant use of two or more antidepressant became more common (Figure 2B). These patterns were largely consistent across the age groups, however with a tendency of less pre-diagnostic psychopharmacological treatment among the young (aged 18-29), with the exception of treatment with SSRIs.

Compared to males, more females had received psychopharmacological treatment in the two years preceding the diagnosis of bipolar disorder (Figures S1 and S2). Those with a prior diagnosis of mental disorder (62.5% of the females with bipolar disorder and 54.5% of the males) were also more likely to have received psychopharmacological treatment compared to those without a prior diagnosis (Figures S3-S6). The same was the case for those with a prior diagnosis of unipolar depression (predominantly driven by treatment with antidepressants).

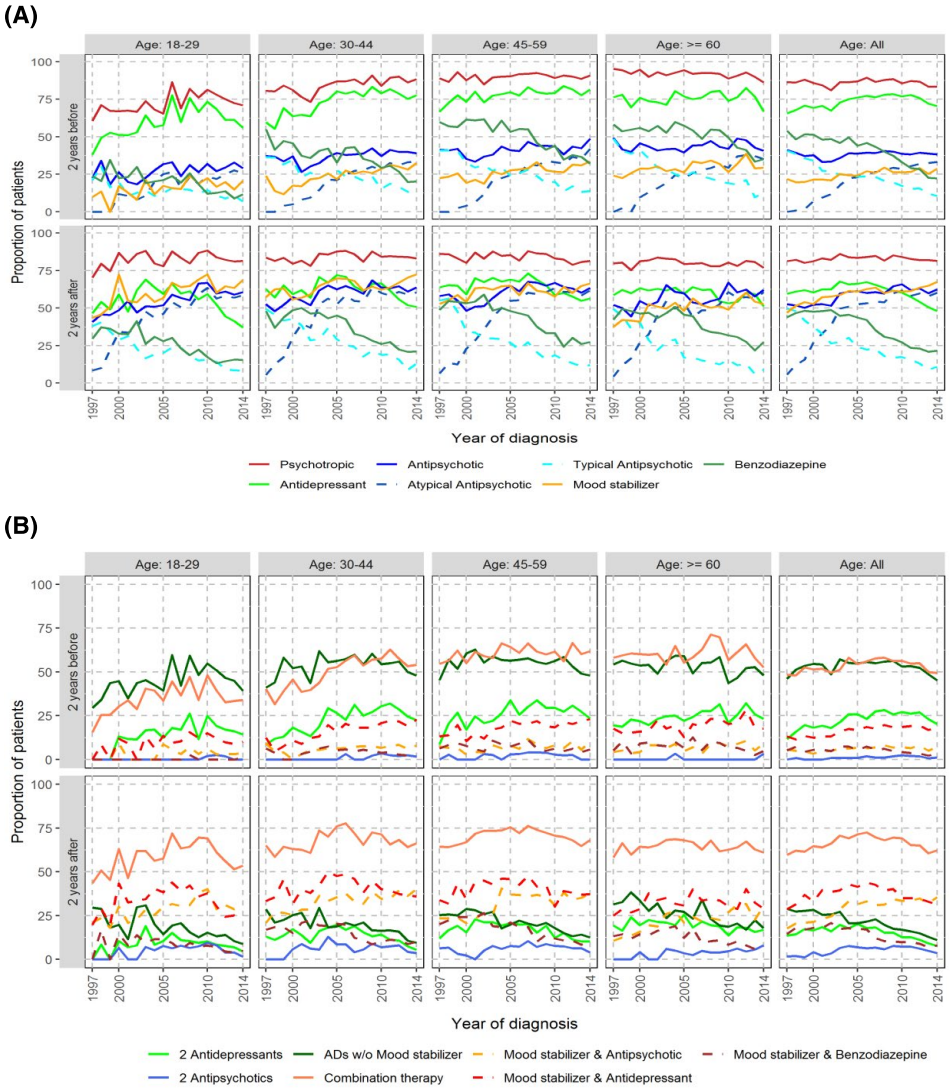


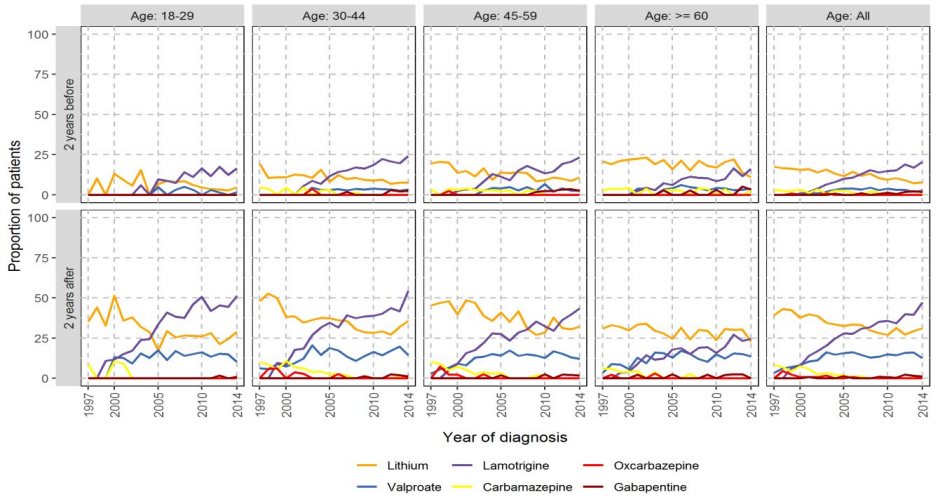
FIGURE 2 Proportion of patients (n = 16 288) using psychotropic drugs from various classes (A) and combinations of drugs (B) in the 2 years before (top panels) and the 2 years after (lower panels) their first bipolar disorder diagnosis. The graphs show for each calendar year the proportion of patients (with index date in the respective calendar years) who were prescribed psychopharmacological treatment in the 2 years preceding (top panel) and the 2 years following (lower panel) the date of the first diagnosis of bipolar disorder. In order to preserve anonymity, observations consisting of less than five patients receiving a particular treatment, or less than five patients not receiving a particular treatment, were set to zero and all patients, respectively

3.2 | Pharmacological treatment following the diagnosis of bipolar disorder in 1997-2014

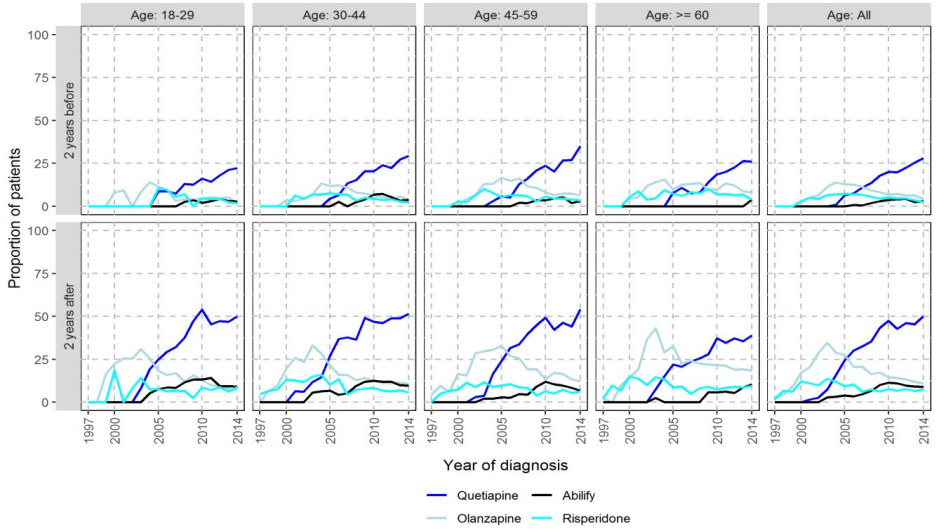
The changes observed over the study period for the pharmacological treatment in the 2 years following the diagnosis of bipolar disorder were somewhat similar to those observed for the 2-year period preceding the diagnosis. Specifically, (i) the use of typical antipsychotics was replaced by use of atypical antipsychotics (Figure 2A)—especially quetiapine and olanzapine, the latter peaking between 2000 and 2005 (Figure 3B); (ii) the use of benzodiazepines was reduced (Figure 2A); and (iii) the use of SNRIs increased while the use of TCAs was reduced (Figure 3C). Furthermore, there was a marked increase in the use of lamotrigine (approaching 50% of all individuals diagnosed in 2014) and

FIGURE 3 Proportion of patients (n = 16 288) using specific mood stabilizers (A), antipsychotics (B) and antidepressants (C) in the 2 years before (top panels) and the 2 years after (lower panels) their first bipolar disorder diagnosis. The graphs show for each calendar year the proportion of patients (with index date in the respective calendar years) who were prescribed psychopharmacological treatment in the 2 years preceding (top panel) and the 2 years following (lower panel) the date of the first diagnosis of bipolar disorder. In order to preserve anonymity, observations consisting of less than five patients receiving a particular treatment, or less than five patients not receiving a particular treatment, were set to zero and all patients, respectively

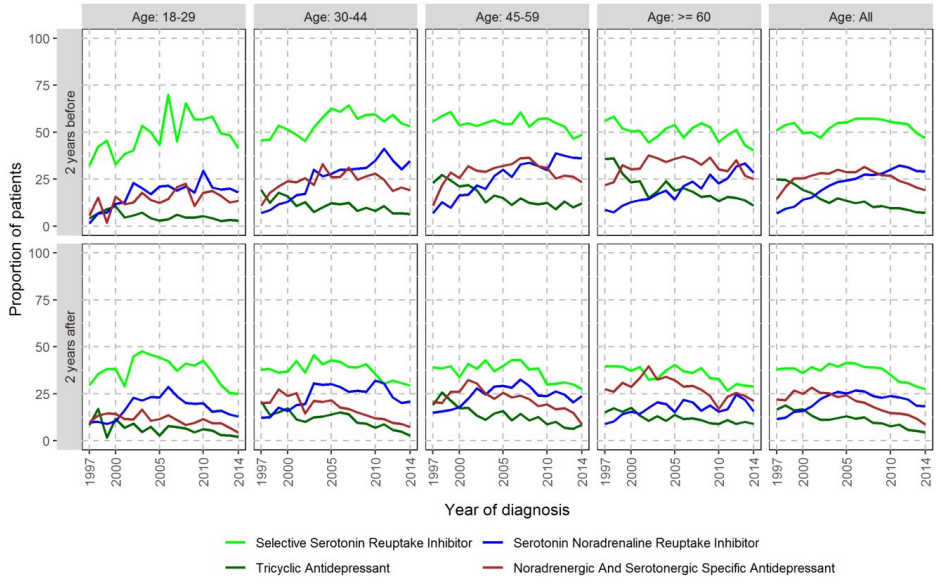
(A)


Age: 18-29
Age: 30-44
Age: 45-59
Age: >= 60
Age: All
2 years before
2 years after
Proportion of patients
Year of diagnosis
Lithium
Lamotrigine
Oxcarbazepine
Valproate
Carbamazepine
Gabapentine

(B)


Age: 18-29
Age: 30-44
Age: 45-59
Age: >= 60
Age: All
2 years before
2 years after
Proportion of patients
Year of diagnosis
Quetiapine
Abilify
Olanzapine
Risperidone

(C)


Age: 18-29
Age: 30-44
Age: 45-59
Age: >= 60
Age: All
2 years before
2 years after
Proportion of patients
Year of diagnosis
Selective Serotonin Reuptake Inhibitor
Serotonin Noradrenaline Reuptake Inhibitor
Tricyclic Antidepressant
Noradrenergic And Serotonergic Specific Antidepressant

valproate while the use of lithium was reduced (only 25%-30% at the end of the study period) (Figure 3A).

The use of drug combinations (concomitant treatment with two different psychotropic drugs) was highly prevalent throughout the study period (approximately 60%-75% of the patients) with increasing use of the combination of a mood stabilizer and an antipsychotic and a slight increase in the use of two antipsychotics in combination (Figure 2B) with the most prevalent combinations being quetiapine + olanzapine and quetiapine + aripiprazole.

Notably, the use of antidepressants was consistently very common among the patients with bipolar disorder (>50% of the patients) over the study period (Figure 2A)—with a substantial fraction (10%-30%) receiving an antidepressant without concomitant treatment with a drug with mood-stabilizing properties (Figure 2B).

Following the diagnosis of bipolar disorder, the pharmacological treatment was largely similar across age groups (Figures 1-3) and for females vs males (Figures S1 and S2). For those with a prior diagnosis of mental disorder, a marked drop in the use of antidepressants was seen when comparing the pre-diagnostic to the post-diagnostic phase (although antidepressants were still commonly used post-diagnostically), with an equivalent rise in the use of mood stabilizers (Figures S3A).

3.3 | Psychopharmacological treatment up to 16 years prior to and 10 years following diagnosis

Nineteen percent of this subcohort used psychotropic drugs already 16 years prior to their bipolar disorder diagnosis, mainly antidepressants and benzodiazepines/hypnotics (Figure 4). The increase in psychotropic drug use in the year leading up to the bipolar disorder diagnosis was primarily driven by use of antidepressants (including two or more antidepressants used concomitantly). In the year following the diagnosis of bipolar disorder, there was a sharp increase in the use of mood stabilizers and antipsychotics and a decline in the use of antidepressants, which however remained relatively prevalent throughout the 10 years post-diagnosis. In the 10 years following the diagnosis of bipolar disorder, treatment with

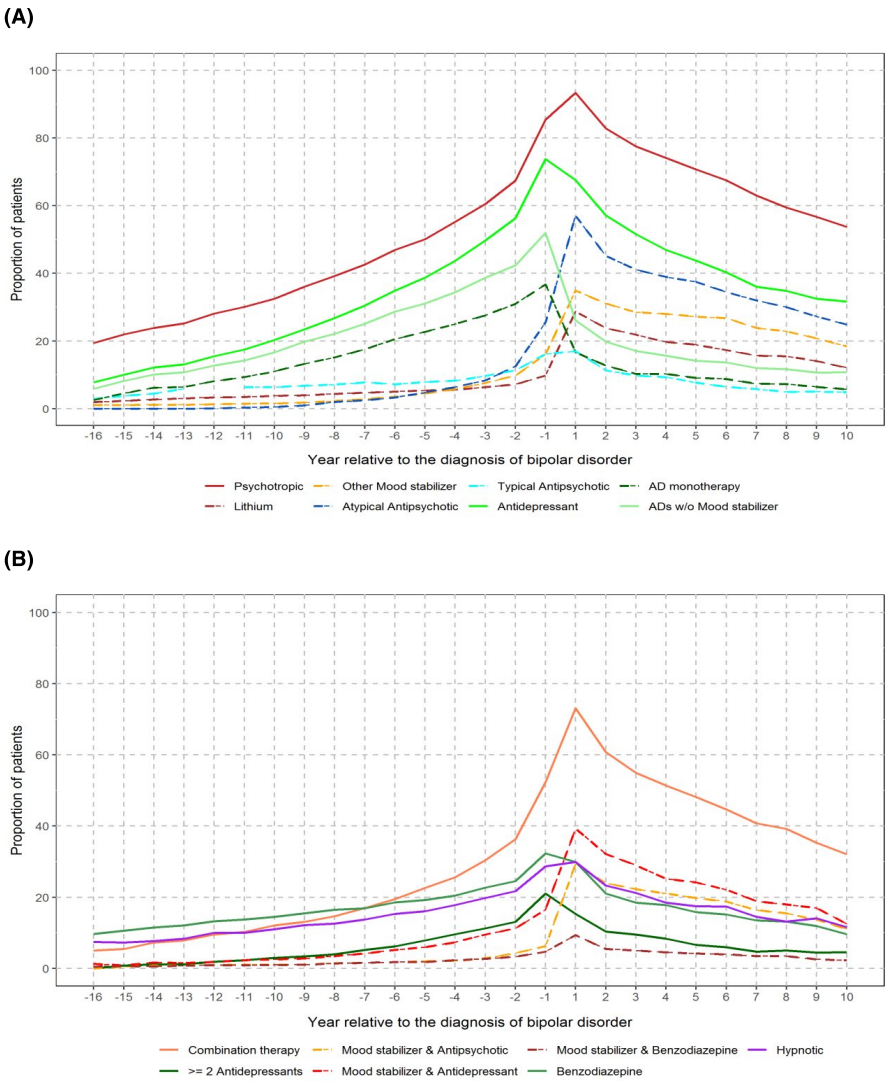


FIGURE 4 Proportion of patients (n = 3949) using mood stabilizers, antidepressants (A), and other psychotropic drugs including combinations (B) in the 16 years prior to and 10 years following their first diagnosis of bipolar disorder (all diagnosed in the period from 2007 to 2010). The mean age at diagnosis for this subpopulation was 45.6 (SD = 16.6) years and 2264 (57.5%) were females

an antidepressant without overlapping use of a drug with mood-stabilizing properties was observed between 26% (1 year after the diagnosis) and 12% (10 years after) of the patients. Ten years after the diagnosis of bipolar disorder, 53% of the patients used a psychotropic drug, and 32% used two or more drugs concomitantly.

4 | DISCUSSION

This study is the first to comprehensively investigate the psychopharmacological treatment both before and after the diagnosis of bipolar disorder in a nationwide sample of patients. The main findings can be summarized as follows: (i) The hospital-based incidence of bipolar disorder more than doubled over the study period (1997-2014); (ii) concomitant use of two or more antidepressants in the 2 years preceding the diagnosis of bipolar disorder increased over the study period; (iii) In the 2 years following the diagnosis of bipolar disorder, the use of lithium decreased while the use of atypical antipsychotics, valproate, and lamotrigine increased over the study period; (iv) the use of antidepressants remained highly prevalent (≈50%) in the 2 years after the diagnosis of bipolar disorder; and (v) in a substantial proportion of cases (between 12% and 26% in the 10 years following the diagnosis of bipolar disorder), antidepressants were used without concomitant treatment with a drug with mood-stabilizing properties.

We observed that the treated incidence of bipolar disorder more than doubled over the study period among both males and females. These results are highly unlikely to represent actual increases in the incidence of bipolar disorder, but rather reflect that the psychiatric hospital system in Denmark has changed during this period—with a large expansion of outpatient services—allowing for a larger intake of patients. In addition, an increased focus on bipolar disorder during the last decades may further explain this increase, particularly in the young individuals. Consequently, an increasing number of individuals have undergone diagnostic assessment at a younger age over this period of time. Also, the mean age at the time of the diagnosis of bipolar disorder decreased substantially from 1997 (54.5 years) to 2014 (40.8 years). The high age at diagnosis compared to other studies reflects that we did not include children and not employ an upper age limit, hence also including individuals with late onset/diagnosed bipolar disorder.[31] The decreasing mean age at the diagnosis of bipolar disorder is likely to lead to improved prognosis, due to decreased duration of untreated illness.[22] However, when assessing the pharmacological treatment in the years prior to the diagnosis of bipolar disorder, it seems evident that there may be ways to decrease the duration of untreated illness even further. Specifically, we observed that the use of two or more antidepressants became increasingly prevalent in this pre-diagnostic phase over the study period. This pharmacological regimen most likely reflects that patients are being (unsuccessfully) treated for treatment-resistant (unipolar) depression, which was actually—in hindsight—bipolar depression. It is well established that bipolar depression may be mistaken for treatment-resistant unipolar depression.[32] The results of the present study suggest that this also occurs in Danish psychiatric services and that a perceived "need" to prescribe an additional antidepressant due to lack of response should automatically lead to thorough screening for bipolar disorder.[33]

Treatment with antidepressants remained highly prevalent once bipolar disorder had been diagnosed, despite the fact that the evidence base for any benefit of this practice is questionable.[34] Somewhat surprisingly, treatment with an antidepressant without concomitant treatment with a drug with mood-stabilizing properties was used between 12% and 26% during the 10 years after the bipolar disorder diagnosis, despite the significant concerns over this practice listed in most major treatment guidelines [1-3] due to increased risk of treatment-emergent affective switches (manic or mixed episodes).[35] Ideally, this finding should lead to changes to clinical practice (no treatment with antidepressants without concomitant mood-stabilizing treatment). Also, it would seem worthwhile to investigate whether this problem exists in other treatment settings than the Danish.

In line with several other studies on the treatment of bipolar disorder,[7,8,13] we found that the use of lithium has decreased over the past decades, seemingly replaced by atypical antipsychotics, valproate, lamotrigine—and combinations of these. While the atypical antipsychotics, valproate, and lamotrigine have mood-stabilizing properties and are recommended by clinical guidelines,[1-3] there is some evidence to support that lithium may be the superior mood stabilizer in the long term [36] and that it may even have specific anti-suicidal effects.[37] Therefore, the decline in lithium use does not seem to be evidence based, but rather reflects barriers to lithium prescription (eg, the need for therapeutic monitoring via blood samples and side effects related to thyroid and kidney function [5,6]) as well as successful marketing of the atypical antipsychotics. This is an unfortunate development.

There are limitations to this study, with the most important relating to the register-based design. First and foremost, the patients with bipolar disorder in this sample were not necessarily diagnosed using research-based assessments. Rather, the diagnoses were assigned as part of normal clinical practice at psychiatric hospitals and registered in the Danish Psychiatric Central Research Register.[24] However, the validity of the bipolar disorder diagnosis in the Register is very high.[38] The same is the case for the diagnoses of unipolar depression [39] and schizophrenia.[40] Relatedly, there are limitations associated with our register-based operationalization of drug treatment. Specifically, the Danish National Prescription Registry only covers redeemed prescriptions.[26] Hence, we have no information on drugs that were prescribed, but where these prescriptions were not subsequently filled. Furthermore, since 2008, a small fraction of patients with bipolar disorder in Denmark (those treated in forensic settings or under compulsory treatment) have received free medication from hospital pharmacies and these dispensations are unfortunately not registered in the Danish National Prescription Registry.[26] The same goes for pharmacological treatment during admissions. Taken together, the existence of these dark figures likely signifies that the proportions of patients with bipolar disorder treated with various drugs, reported in this study,

are slightly underestimated. The most important strength of the study lies in its register-based approach that allowed us to follow a nationwide representative population of more than 16 000 patients in the time period (up to 21 years) surrounding their diagnosis of bipolar disorder.

With regard to generalizability, we have no reason to believe that the individuals with bipolar disorder in this cohort should differ substantially from those seen in hospital psychiatry in other developed countries with regard to psychopathology and need for psychopharmacological treatment. However, even though the primary Danish treatment guideline for bipolar disorder is well in line with international guidelines,[41] our findings will likely not translate 1:1 to all other countries. For instance, the use of lithium in Denmark (although declining) is more common compared to, for example, the United States.[41] That being said, the overall pattern of changes in psychopharmacological treatment over the past two decades observed in the present study is largely consistent with that observed in studies from other countries,[11,42] which do however not cover the pre-diagnostic phase.

In conclusion, this study found that the incidence of hospital-diagnosed bipolar disorder has more than doubled in Denmark over the past two decades and that patients were diagnosed at a younger age—likely translating into reduced duration of untreated illness. Nevertheless, our findings of increased concomitant use of two or more antidepressants in the years preceding the diagnosis of bipolar disorder suggest that the duration of untreated illness can be shortened even further by implementing more effective screening for bipolar disorder in the case of treatment-resistant "unipolar" depression. Furthermore, our observations of (i) declining use of lithium, (ii) increased use of drug combinations with little/no empirical support, and (iii) prevalent use of antidepressants without overlapping treatment with a drug with mood-stabilizing properties in the treatment of bipolar disorder are worrying and should lead to reconsiderations of clinical practice.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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